



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/62, C07K 14/725, 16/28, G01N G01N 33/68, A61K 38/17, C07K 19/00	A3	(11) International Publication Number: WO 96/21028 (43) International Publication Date: 11 July 1996 (11.07.96)
(21) International Application Number: PCT/US95/16937 (22) International Filing Date: 28 December 1995 (28.12.95) (30) Priority Data: 08/367,589 3 January 1995 (03.01.95) US (71) Applicant: PROCEPT, INC. [US/US]; 840 Memorial Drive, Cambridge, MA 02139 (US). (72) Inventors: BANERJI, Julian; 37 Lincoln Street, Lincoln, MA 01773 (US). KHANDEKAR, Sanjay; 72 Grassland Street, Lexington, MA 02173 (US). BRAUER, Pamela; 21 Gedney Court, Salem, MA 01970 (US). NAYLOR, Jerome; 99 Marion Street, Somerville, MA 02143 (US). MCKEEVER, Una; 36 Robinwood Avenue #1, Boston, MA 02130 (US). JESSON, Michael; 19 Plain Street, Hopedale, MA 01747 (US). JONES, Barry; 341 Gurney Street, Cambridge, MA 02138 (US). (74) Agents: CARROLL, Alice, O. et al.; Hamilton, Brook, Smith & Reynolds, Two Militia Drive, Lexington, MA 02173 (US).		(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 12 September 1996 (12.09.96)
(54) Title: SOLUBLE HETERODIMERIC T CELL RECEPTORS AND THEIR ANTIBODIES		
(57) Abstract <p>Heterodimeric T cell receptor proteins, comprising α and β subunits joined by at least one disulfide bond, are disclosed. The α and β subunits are generated as chimeric polypeptides, utilizing ζ chains or constant regions of IgG1 as chimeric partners. Also disclosed are soluble heterodimeric T cell receptor molecules with a conformation essentially indistinguishable from that appearing on the surface of T cells. The invention also concerns DNA encoding the heterodimeric TCR, transfer vectors comprising DNA encoding the heterodimeric TCR, and host cells containing such transfer vectors. In addition, the invention pertains to various uses of heterodimeric TCR. The proteins can be used in molecular assays designed to measure their binding to ligands, including MHC/HLA-peptide antigen complexes or TCR-specific antibodies. Such assays are useful for the detection of agents that block the TCR-ligand interaction. The heterodimeric TCR can also be used to immunize animals, including humans, to produce TCR-specific antibodies. In addition, either in their native or denatured conformation, the proteins can be used to vaccinate animals, including humans, in order to suppress the immune response of T cells bearing TCR that share antigenic epitopes with the vaccinating protein.</p>		

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INTERNATIONAL SEARCH REPORT

International Application No

PC1/US 95/16937

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/62 C07K14/725 C07K16/28 G01N33/68 A61K38/17
C07K19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 12648 (INST NAT SANTE RECH MED ;IMMUNOTECH SA (FR); BONNEVILLE MARC (FR)) 9 June 1994	1,2, 9-11,18, 20-38
Y	see the whole document	1-3,5,6, 8-12,14, 15,17-38

X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 91, August 1994, WASHINGTON US, pages 8462-8466, XP002008360 J. KAPPLER ET AL: "Binding of a soluble alpha-beta T-cell receptor to superantigen/major histocompatibility complex ligands"	1,2, 9-11,18, 20,21, 24-27
Y	see the whole document	22,23, 28-38

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

15 July 1996

Date of mailing of the international search report

23.07.96

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INTERNATIONAL SEARCH REPORT

Inter onal Application No

PC1/US 95/16937

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCIENCE, vol. 256, 29 May 1992, pages 1318-1321, XP002008361 I. ENGEL ET AL: "High-efficiency expression and solubilization of functional T cell antigen receptor heterodimers"	1-4,6,7, 9-13,15, 16,18-21
Y	see the whole document ---	22-38
X	WO,A,92 01715 (UNIV LELAND STANFORD JUNIOR) 6 February 1992	1-3,6, 9-12,15, 18-21
Y	see the whole document	22,23, 29-38
X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 91 (24). 1994. 11408-11412. ISSN: 0027-8424, XP002008362 CHANG H-C ET AL: "A general method for facilitating heterodimeric pairing between two proteins: Application to expression of alpha and beta T - cell receptor extracellular segments."	1-3,6, 9-12,15, 18-21
Y	see the whole document	22,23, 29-38
X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 91, December 1994, WASHINGTON US, pages 12862-12866, XP002008363 K. MATSUI ET AL: "Kinetics of T-cell receptor binding to peptide/I-Ek complexes"	1,2, 9-11, 18-21, 24,25
Y	see the whole document	22,23, 26-38
X	NATURE, vol. 356, 30 April 1992, pages 793-796, XP002008364 S. WEBER ET AL: "Specific low-affinity recognition of major histocompatibility complex plus peptide by soluble T-cell receptor"	1-3,5,6, 8-12,14, 15, 17-21, 24,25
Y	cited in the application see the whole document	22,23, 26-38

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INTERNATIONAL SEARCH REPORT

International Application No

PC1/US 95/16937

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 89, August 1992, WASHINGTON US, pages 6871-6875, XP002008365 D. EILAT ET AL: "Secretion of a soluble, chimeric gamma-delta T-cell receptor-immunoglobulin heterodimer" see the whole document ---	1-3,5,6, 8-12,14, 15,17-38
Y	JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, no. 21, 25 July 1993, MD US, pages 15455-15460, XP002008366 F.DAVODEAU ET AL: "Secretion of disulfide-linked human T-cell receptor gamma-delta heterodimers" see the whole document ---	1,2, 9-11, 18-38
Y	WO,A,93 12814 (IMMUNE RESPONSE CORP INC) 8 July 1993 see the whole document ---	22,23, 29-38
P,X	IMMUNOLOGIST (1995), 3(2), 59-66 CODEN: INOLEG;ISSN: 1192-5612, March 1995, XP000575900 WULFING, CHRISTOPH ET AL: "Soluble T - cell receptor fragments. Guidance of folding and assembly" see the whole document -----	1-21
Y	see the whole document -----	22-38

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/ 16937

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 22,23 and 29-38 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/16937

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9412648	09-06-94	FR-A- 2698880	10-06-94
		AU-B- 5566894	22-06-94
		CA-A- 2128705	09-06-94
		EP-A- 0624201	17-11-94
		JP-T- 7506495	20-07-95

WO-A-9201715	06-02-92	NONE	

WO-A-9312814	08-07-93	AU-B- 3418893	28-07-93
		CA-A- 2126686	08-07-93
		EP-A- 0623025	09-11-94
		JP-T- 7506563	20-07-95
